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APPARATUS FOR PREDICTING BONE FRACTURE RISK

The present invention relates to apparatus for predicting bone fracture risk, in particular for predicting bone
5 fracture risk in an osteoporotic patient.

Osteoporosis (OP) is a disease of the bones in which a reduction in bone density causes bone weakness. A patient is defined as suffering from OP by the World Health Organisation
10 if their bone mineral density (BMD) is less than 2.5 standard deviations below the young mean value, BMD being a measure of the quantity of bone in a given volume or area. In OP, bone material is gradually lost, until the bone becomes so weak as to be susceptible to fracture at
15 relatively low impacts.

The current best method for measuring BMD is believed to be Dual X-ray Absorptiometry (DXA). DXA is used both for the diagnosis of OP and for assessment of treatment efficacy. DXA
20 systems employ two X-ray beams of different energies. BMD is calculated from the absorption of each X-ray beam by bone, after subtracting absorption by soft tissue. A digital image can be produced on a display attached to the DXA scanner, the pixel value at any point representing the BMD value.
25

Patients are often unaware that they are suffering from OP, since there are few or no warning signs until a fracture actually occurs, unless a bone scan has been performed. OP treatment is generally assessed either in terms of fracture
30 prevention, or by increases in BMD, as an indicator of fracture prevention.

A common fracture site in OP patients is the hip, i.e. the

proximal femur. The shape of the proximal femur is known to be an important factor in predicting fracture in OP patients. Images of the proximal femur for shape analysis are typically obtained from radiographs, i.e. "normal" X-rays.

5

Traditionally, proximal femur shape has been measured geometrically, for example by measuring the femoral neck length, the neck shaft angle, or the cross sectional moment of inertia. Alternatively, proximal femur shape can be

10 assessed using finite element models, i.e. computer software-generated engineering models which divide an image of the femur into "elements", and calculate the forces in each element generated by applying a given force at a particular point.

15

However, both geometric and finite element analyses of femur shape have limitations. Thus, geometric measurements are easy to obtain and analyse, but only provide an analysis of individual components in a complex structure: the strength

20 of the femur, and hence the risk of fracture, is affected by all of the structural features, and their interaction with each other. Furthermore, it is difficult to extrapolate the effects of changes in individual measurements, since each individual measurement is not only correlated with every

25 other measurement, but also with factors such as the height and weight of the patient. In contrast, finite element analysis is computationally expensive, with a separate model being created and tested for each patient.

30 Attempts have also been made to measure bone strength, by "texture" analysis, i.e. by quantifying bone structure rather than bone shape. Such analyses have been performed on radiograph images, for example, from visual scoring systems,

such as the Singh index, to more sophisticated computerised techniques based on fractal analysis and other image processing methods. Recently, fractal analysis has been the predominant method of texture analysis, although it has not
5   categorically been established as preferable to other methods of texture analysis.

The present invention seeks to provide apparatus for predicting fracture risk in OP patients which overcomes the
10 aforementioned limitations of known approaches to fracture risk analysis.

According to the present invention there is provided apparatus for predicting bone fracture risk in an
15 osteoporotic patient, which apparatus comprises a Dual X-ray Absorptiometry scanner for scanning a body part of the patient and producing a Dual X-ray Absorptiometry image of the body area; image analysis means for analysing pre-determined aspects of the Dual X-ray Absorptiometry image,
20 the aspects being pre-determined according to the body part being scanned, and for generating an image data set from the Dual X-ray Absorptiometry image; and data comparison means comprising a database of comparative data sets from Dual X-ray Absorptiometry images of control subjects, for comparison
25 with the image data set for the Dual X-ray Absorptiometry image of the patient, to thereby predict the risk of bone fracture in the patient.

The present invention thus provides apparatus which can be
30 used to simply and easily predict the risk of bone fracture in a patient without the need for expert analysis of the DXA image. By pre-determining the aspects of the DXA image which are to be analysed, and by having a database of comparison

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data sets from control subjects for those aspects already
stored in the apparatus, the apparatus of the present
invention can automatically provide a prediction of fracture
risk in the patient. The control subjects preferably comprise
5 both fracture and non-fracture subjects.

The apparatus of the present invention comprises a Dual X-ray
Absorptiometry (DXA) scanner for scanning a body part of a
patient and producing a DXA image of that body part. Any
10 suitable DXA scanner may be used, as are commercially
available and known in the art.

The apparatus of the present invention also comprises image
analysis means for analysing pre-determined aspects of the
15 DXA image. The aspects of the image to be analysed are pre-
determined according to the part of the body being scanned.
Thus, the aspects of an image of a proximal femur for
analysis will be different from those of a wrist, ankle,
hand, spine, and so forth. Thus, if the apparatus is to be
20 used for predicting fracture risk in the proximal femur of
a patient, then the particular pre-determined aspects of a
proximal femur image are those which will be analysed by the
image analysis means.

25 The image analysis means preferably analyses the DXA image
by analysis of the shape of the particular body part or by
analysis of the texture of the body part.

A preferred method of shape analysis is by use of an Active
30 Shape Model. An Active Shape Model (ASM) is an image
processing model which can be used to analyse shapes which
have common features, but which are subject to natural
variation, such as a human body part. An ASM is a

mathematical model which can be used to quantify differences
in the shape of a body part, for example the proximal femur,
between an OP patient, and a control subject.

5 As discussed above, the image analysis means used in the
present invention analyses pre-determined aspects of the DXA
image. In those preferred embodiments in which the image
analysis means uses an ASM, a model is built to measure
those particular aspects of the image, and is stored in the
10 apparatus. The particular model which is built will thus be
different for each different body part being analysed, since
each different body part has different significant aspects
for analysis.

15 Thus, using an ASM, a number of landmark points (i.e.
aspects) of the DXA image are selected for analysis to
determine the outline of a particular body part, i.e. a
model is built. Thus, for a proximal femur the landmark
points may include, for example, the tip of the greater
20 trochanter, and the narrowest point of the femoral neck. The
coordinates of these points are measured and used to
calculate the morphometry of the body part, i.e. a data set
for that ASM is generated.

25 In a given particular model, a number of independent shape
variation components may be produced by the ASM, some or all
of which may be associated with fracture. For example, where
a proximal femur shape is being analysed, each of the
components may describe a characteristic of the shape of the
30 femur, and may combine features such as the hip axis length
and neck-shaft angle. For a particular model, discriminant
analysis is preferably applied to determine which variable
or combination of variables is best able to predict fracture

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risk. An ASM has an advantage over conventional geometrical analysis of bone shape in that the whole outline of the bone is measured, through pre-determined landmark points, rather than individual geometrical properties.

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The ASM data set generated from the DXA image of the patient may be compared with the comparative data sets in the database, for example by examining how the location of the landmark points deviates from the mean co-ordinates of the

10 comparative data sets, from which fracture risk may be predicted.

A preferred toolkit for producing ASMs for use in the apparatus of the present invention is the ASMTk from Visual

15 Automation Limited, Manchester, UK, which runs within the MATLAB software environment (The MathWorks Inc., Natick, USA).

An alternative preferred means of analysis by which the image

20 analysis means used in the present invention may analyse the DXA image is by analysis of the texture of the body part.

A preferred method of texture analysis uses Fourier transforms and Principal Component Analysis to generate a

25 mathematical model of the DXA image data.

Principal Component Analysis (PCA) is a data reduction technique which describes data in terms of orthogonal, linearly independent components. A relatively small number

30 of components, comprising linear combinations of the original variables, thus contain the majority of the information. PCA has no preconditions, such as relying on the data to fit a normal or fractal distribution, but builds a mathematical

model based on the correlations present in the data, which can then be used to investigate the similarities and differences between bone structure, for example trabecular bone structure, in a patient and a control group.

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In preferred embodiments of the present invention which use texture analysis to analyse the DXA image, the DXA image is preferably digitised and regions of interest identified in the image. For example, where a proximal femur is being
10 analysed, the regions of interest may, for example, be located at the femoral head and neck. A power spectrum may be obtained from a Fourier transform of each region of interest, and profiles of each region produced. PCA may then be used to generate a data set from each profile, which can
15 be compared with the database of comparative data sets.

The image analysis means used in the apparatus of the present invention may use one or more image analysis methods. Thus, the image analysis means may use both shape and
20 texture analysis, as described above. For example, the image analysis means may analyse the DXA image using both an ASM and Fourier transforms and Principal Component Analysis.

The apparatus of the present invention comprises data
25 comparison means comprising a database of comparative data sets from Dual X-ray Absorptiometry images of control subjects, for comparison with the image data set for the Dual X-ray Absorptiometry image of the patient, to thereby predict the risk of bone fracture in the patient. Thus, a
30 series of DXA images of control subjects are taken, for example in the case of fracture risk prediction in OP patients the control subjects would be persons not suffering from OP, and analysed by the image analysis means to

generate a data set for the DXA image of each control subject. For example, if the image analysis means uses an ASM, then the same ASM is used to analyse each of the DXA images of the control subjects. If the image analysis means uses both an ASM and Fourier transforms and Principal Component Analysis, then both of these methods of image analysis are performed on each of the DXA images of the control subjects. In this way, a database of comparative data sets from the control subjects is created, and stored in the apparatus, appropriate to the method of image analysis being used to analyse the DXA image of the patient.

The apparatus of the present invention may be used for predicting fracture risk in different body parts, for example the proximal femur, wrist, ankle, hand or spine. Each different body part will have significant aspects for analysis, for example landmark points when using shape analysis, or regions of interest when using texture analysis, and these aspects are predetermined and stored in the apparatus. In addition, a database of comparative data sets from control subjects for those aspects for each body part is also stored in the apparatus. In use, the operator thus initially merely selects which body part is to be analysed, and the apparatus accordingly selects the appropriate aspects of the DXA image for analysis, and the appropriate database of comparative data sets for comparison therewith.

The apparatus of the present invention uses DXA image analysis to predict fracture risk. As discussed above, DXA images are conventionally used for determining BMD. Accordingly, the fracture risk prediction value determined by the image data set comparison may used in combination with the standard BMD data obtained from the DXA image, to

provide a more accurate prediction of fracture risk. Thus, the apparatus of the present invention may be used to accurately predict fracture risk by comparing the results of ASM and Fourier transforms and Principal Component Analysis
5 of the DXA image, together with the standard BMD data obtained directly from the DXA image.

Although the apparatus of the present invention is principally directed to predicting fracture risk in OP
10 patients, it is not limited in application thereto, and may also be applied for use with patients with other disorders which affect the shape or trabecular structure of bone. For example, the apparatus of the present invention may be used to measure the progress of osteoarthritis or Paget's disease,
15 by quantifying the deformation of the femur. The apparatus may also be used for measuring non-pathological changes in a subject associated with age, gender, body mass index and/or genetics.

20 Embodiments of the present invention will now be described in detail with reference to the accompanying drawings in which:

Figure 1 shows a typical radiograph of the proximal femur
25 showing the positions of landmark points for different Active Shape Models to be used to analyse the shape of the femur: (a) Model 1, 10 points (b) Model 2, 10 points (c) Model 3, 20 points (d) Model 4, 29 points);

30 Figure 2 shows landmark points on a typical radiograph of the proximal femur for Active Shape Model 5, from which geometrical measurements were also obtained by calculating the distance between numbered landmark points, viz. Neck

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Length (N-Len) between points 11 and 26, Neck Width (N-Wid)
between points 4 and 18, and Head Diameter (H-Diam) between
points 16 and 8; and

5 Figure 3 shows a typical radiograph of the proximal femur
showing how regions of interest (ROIs) for texture analysis
can be located by points A to G, determined by the femoral
head and neck, Points A and E marking the femoral neck
width, Points B, C and D lying at 25%, 50% and 75% along
10 this line, Point F being the centre point of the femoral
head, and Point G being half the diameter of the femoral
head at an angle of 45 degrees to the neck width, 135
degrees to the neck shaft, shown as a grey dashed line.

15 <u>Example 1</u>
   <u>A) Materials and Methods</u>
   <u>I) Image acquisition</u>
   Data were taken from a previous study [Stewart, A., Black,
   A., Robins, S. P., and Reid, D. M. Bone Density and Bone
20 Turnover in Patients with Osteoarthritis and Osteoporosis.
   J Rheumatol 1999 263:622-626]. Although this study had
   included subjects with osteoarthritis, they were excluded,
   leaving 30 patients who had sustained a hip fracture at
   least 3 years prior to DXA examination and 30 control
25 subjects matched for age. All patients had undergone a scan
   of their unfractured hip and a total body scan by DXA using
   a Norland XR-26 scanner. The controls had had their left hip
   scanned. Five BMD and Bone Mineral Content (BMC) values were
   used: total body BMD, total body BMC, femoral neck BMD (NECK
30 BMD), trochanteric BMD (TROCH BMD) and Ward's triangle BMD
   (WARDS BMD). A pelvic antero-posterior radiograph, which had
   been recorded within a year of the DXA scan, was also used.
   All subjects were ambulant out-patients at the time of study

and did not have increased bone turnover as assessed by pyridinoline/creatinine and deoxypyridinolone/creatinine ratios, so that immobility induced or post-fracture osteopenia is unlikely.

The Radiographs were digitised using a Howtek MultiRAD 850 scanner (Howtek, Hudson, New Hampshire) at a resolution of 73 dpi (348 mm per pixel) and a depth of 8 bits. The quality of the digitised radiographs was assessed and the image was discarded if the outline of the femur below the greater trochanter was not wholly visible on the radiograph, or if the image the outline could not properly be identified. This left a dataset of 50 images; 26 hip fracture patients (HIP) and 24 controls (CNT).

II) Active Shape Model (ASM) Design

An ASM of the proximal femur was created using an active shape modelling toolkit (ASMTk) (Visual Automation Limited, Manchester, UK), a software program which runs within the MATLAB (The MathWorks Inc, Natick, USA) software environment. A representative subset of the images was chosen as a training set. A series of landmark points which identify key features of the femur, including the tip of the greater trochanter and the narrowest point of the femoral neck, were marked on each image. The same number of landmark points was used for each image in the model and each point always refers to the same feature in the shape. The software first aligned the shapes by scaling, rotating and translating them in order to minimise the variance, in distance, between equivalent points. This process means that all data about the shape is stored proportionally, rather than absolutely, and the effects of the overall size of the femur on measurements such as neck length, neck width and shaft width are

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eliminated. The size of the femur was recorded as the ratio between the area of the outline and the average area of all the outlines and saved as a separate variable, Fscale.

5 Twenty images were randomly selected to create a training set. Five different models were created, using different numbers of landmark points, and tested for relative accuracy and repeatability. The landmark points were marked manually for each model on each image. Model 1 (Figure 1a) comprised
10 10 landmark points which mark the main femoral axes, as are used in studies of femoral geometry. These corresponded to the neck axis length (distance A-D), the neck width (distance B-J), the shaft width (distance E-I) and the intramedullary diameter (distance F-G). Model 2 (Figure 1b) comprised 10
15 landmark points which describe the main features of the outline including the shaft, femoral head, neck and greater trochanter, but excluding the lesser trochanter, because of its variable appearance related to hip positioning. Models 3 and 4 were more detailed versions of Model 2, comprising
20 20 and 29 landmark points respectively (Figures 1c, 1d). Because the length of shaft visible in the radiographs varied greatly across the subject group, and a number of radiographs showed no part of the shaft below the lesser trochanter, a further model, Model 5 (Figure 2), was designed. Model 5
25 comprised 29 points describing the outline of the femur, including the outline of the lesser trochanter, to compare with its omission from the other models, but excluding the shaft below that region.

30 To compare the models after training, two measures of repeatability were calculated on the training set for each of the models using the ASMTk. Each of the 20 training images was loaded in turn, and the trained model

automatically searched for the outline of the femur, starting from the mean shape and pose. The shape identified automatically by the ASMTk was then compared with the manually labelled shape prepared for the training set using
5 two error estimators. The point-to-point error was calculated as the mean distance, in pixels, between the original, manually generated, points and those automatically generated by the software. The point-to-line error was the mean distance between the automatically generated landmark points
10 and lines tangential to the outline at each of the corresponding points on the manually labelled images.

The best model was thus chosen, and the remaining images were analysed using this model. The independent modes of
15 variation were found for each image using Principal Component Analysis and used as inputs to the statistical analysis. Each mode of variation is a linear combination of the original variables (viz. the x and y co-ordinates of each landmark point) and is selected so as to be orthogonal, and therefore
20 linearly independent, of all the other modes. When combined, the modes of variation account for 100% of the variance in the original data set. Each mode is ordered according to the amount of variation explained: lower numbered modes account for the largest percentage of variance, whilst higher
25 numbered modes, in this case, greater than mode 10, explain little variance and can be treated as noise.

III) Geometrical Analysis

Three conventional geometrical measurements were calculated
30 from the radiographs for comparison: neck axis length (N-Len), femoral neck width (N-Wid) and femoral Head Diameter (H-Diam). These measurements were calculated using the co-ordinates of the landmark points of the ASM (Figure 2).

The geometrical properties of the femur are known to be highly correlated with each other and with the height and weight of an individual, but by using ratios of two measurements instead of single measurements the influence of
5 these effects can be reduced. Thus, compound variables were created, N-Wid/N-Len and H-Diam/N-Len. A number of radiographs used in the study showed little or nothing of the shaft below the lesser trochanter, and so the model used did not analyse the femur below this point. For this reason,
10 neither the width of the shaft or the neck-shaft angle were measured reliably, and these measurements were excluded from the study.

IV) Statistical Analysis

15 All variables were tested for significant differences between the two groups using Student's t-test, if the variable passed a normality test, or a Mann-Whitney Rank Sum test otherwise (SigmaStat 2.0, SPSS Science, Chicago). Stepwise linear discriminant analysis was used to estimate the probability
20 that a given subject would belong to the fracture group. If this probability was greater than 0.5, the subject was assigned to the fracture group. As the modes are generated using Principal Components Analysis, each mode is linearly independent of all other modes, so problems associated with
25 stepwise methods due to multicollinearity are avoided. The probability generated by this process was saved as a new variable, Pshape, for use in combination with BMD values. The same method was also used to create a classifier from the geometrical measurements.
30

Linear discriminant analysis was used to assess both the strength of single variables and combinations of variables. Discriminant analysis was used in conjunction with binary

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logistic regression to calculate the odds ratio associated with each variable. SPSS v10 statistical software (SPSS Science, Chicago) was used for both discriminant and logistic analysis.

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B) Results

I) Model testing

Using the point-to-point and point-to-line errors as estimators of the accuracy of each model, Model 5 was the
10 most accurate (Table 1).

Table 1			
Model	Number of landmark points	Median Point-to-Point Error (mm)	Median Point-to-Line Error (mm)
1	10	8.5	6.6
2	10	5.8	4.2
3	20	3.3	2.0
4	29	3.3	2.0
5	29	2.2	1.3

20 Model 5 located the outline of the femur with a median point-to-point error of 6.22 pixels (2.17 mm) and a median point-to-line error of 3.81 pixels (1.32 mm) when comparing the automatically located points with those inputted manually on the training set. This model was used in the subsequent
25 analysis. The search is reset to start from the same outline each time (the mean shape and position of the outlines stored in the model) and is thus fully automated, being repeatable, finding exactly the same points, each time an image is analysed.

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II) Statistical Analysis

There were no significant differences in the age, height, weight or body mass index between the fracture and control groups.

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All the modes of variation found by the ASMTk were normally distributed and two of the modes (numbers 2 and 7) were significantly different between the two groups ($P < 0.05$, t-test). The size of the femur (Fscale) was not significantly

10 different between the HIP and CNT subjects ($P = 0.34$). Four of the five BMD measurements showed statistically significant differences between the two groups ($P < 0.01$), the exception being Total Body BMD ($P = 0.11$). None of the geometrical measurements or ratios showed statistically significant

15 differences between the two groups. The values found are summarised in Table 3.

Table 3 shows the mean values of all the variables measured from 26 fracture patients (HIP) and 24 controls (CNT) and

20 the significance of the difference between these two groups. The results indicate that the data were not normally distributed (Kolmogorov-Smirnov test), and the Mann-Whitney test was used instead of the t-test and the 25% and 75% confidence limits shown instead of the standard deviation.

25 Variables showing significant differences between the groups are in bold.

Table 3					
Variable	HIP		CNT		P-value
	Mean	SD	Mean	SD	
Bone Mineral Density Measurements					
Neck BMD (gcm^{-2})	0.604	0.066	0.696	0.109	0.001
Total BMC (g)	1883	295	2138	274	0.003
Total BMD (gcm^{-2})	0.92	0.12	0.87	0.10	0.111
Troch BMD (gcm^{-2})	0.493	0.084	0.586	0.078	<0.001
Ward's BMD (gcm^{-2})	0.417	0.073	0.659	0.173	<0.001
Active Shape Model Modes					
Mode 2	7	19	-5	16	0.019
Mode 4	-5	16	2	12	0.107
Mode 5	-4	12	2	12	0.094
Mode 7	3.1	9.7	-2.6	9.7	0.044
Geometric Measurements					
H-Diam	53.7	2.6	52.7	3.1	0.196
N-Len	110.2	5.3	109.7	7.6	0.759
N-Wid	38.2	3.2	37.8	2.8	0.671
Ratios					
N-Wid/N-Len	0.34	0.33	0.34	0.33	0.831
		0.36		0.36	
H-Diam/N-Len	0.49	0.0299	0.48	0.03	0.347

III) Discriminant Analysis

As all the modes of variation were distributed normally, stepwise linear discriminant analysis was used to select the best combination to build a classifier which could distinguish between the fracture and control groups. The discriminant analysis found that the 2nd, 4th, 5th and 7th modes of variation could be combined to build a classifier, Pshape, with 74% accuracy.

Discriminant analysis was carried out on variables Pshape, WARD'S BMD, TOTAL BMD, TOTAL BMC, NECK BMD and TROCH BMD using each as the sole discriminator. As can be seen from Table 4, the Pshape variable (accuracy 74%, area under ROC
5 0.81) was more accurate than most of the BMD measurements, with only WARD'S BMD (accuracy 82%, area under ROC 0.95) being a more powerful classifier, although this difference was not found to be significant by ROC analysis.

10 Table 4 shows the percentage accuracy of classification into fracture or control groups using linear discriminant analysis.

Table 4		
Variable	Accuracy (%)	Area under ROC
Ward's BMD	82	95
Pshape	74	81
Neck BMD	74	79
Total BMC	70	74
Troch BMD	68	79
Total BMD	66	63
Geometric ratio (H-Diam/N-Len)	60	59
Geometric (H-Diam)	58	59
Pshape and Ward's BMD	90	96
Pshape and Neck BMD	82	89

Stepwise discriminant analysis was also used to build
30 classifiers from the geometrical measurements and ratios. None of the geometrical variables were strong enough to be selected by the stepwise analysis. Linear discriminant

analysis was performed on each of these variables independently with the following results: N-Wid (54%), H-Diam (58%), N-Len (56%), N-Wid/N-Len (50%), H-Diam/N-Len (60%). These results show that the geometrical variables were weaker
5 discriminators than either BMD or ASM measurements.

Discriminant analysis was also used to test the ability of different combinations of variables to classify the two groups correctly. By combining the two best individual
10 discriminators, WARDS BMD and Pshape, accuracy was increased to 90% (area under ROC 0.96). Discriminant analysis was also performed using the variables Pshape and NECK BMD to build a classifier. Both Pshape and NECK BMD achieved the same accuracy (74%) when used alone (area under ROC 0.81 and 0.79
15 respectively), whilst the combination of the two variables produced a classifier that was again substantially better than either measurement alone (accuracy 82%, area under ROC 0.89). Comparison of the area under the ROC showed that the improvement gained by adding the Pshape data to Neck BMD was
20 statistically significant (P < 0.05).

Logistic regression analysis showed that Pshape was still an independent predictor of hip factor after adjustment for age, body mass index and WARDS BMD (odds ratio 1.83, 95% CI 1.08-
25 3.113) and also after adjustment for age, body mass index and NECK BMD (odds ratio 1.75, 95% CI 1.21- 2.53). The odds ratios were calculated to represent the increase in the odds linked to a 10% increase in the estimated probability of belonging to the fracture group as calculated from the ASM
30 data.

The use of ASM thus shows that a trained model can be used successfully to discriminate between a fracture and control

group. The ASM alone performs better than most of the BMD
measurements and all of the geometrical measurements. The
best classifier tested combined the ASM data, Pshape, with
WARD'S BMD to create a classifier with 90% accuracy. This
5 was better than WARD'S BMD alone which, in turn, was better
than the ASM data alone. All direct geometrical measures were
inferior. Sensitivity analysis showed that only one of the
fracture cases was missed. Analysis of Pshape with both
Ward's triangle and femoral neck BMD showed that Pshape was
10 independently associated with membership of the fracture
group.

The independent modes of variation found by ASM are
orthogonal and, therefore, each represents a change in the
15 shape that happens independently of other changes. If a mode
of variation is significantly different between the two
groups, it will describe changes in shape affecting the whole
of the proximal femur that potentially influence the
likelihood of fracture. Analysis of these modes allows
20 investigation of interactions, which are not made available
by measuring changes in the individual geometrical properties
of the femur.

Any 2D projection of a 3D structure, such as a DXA or X-ray
25 image of the hip, is sensitive to the effects of rotation,
foreshortening and magnification. Errors in geometrical
measurements due to the position and rotation of the femur,
positioning of the patient in the DXA or X-ray beam or the
thickness of the patient's soft tissue are common and hard
30 to adjust for after the scan. However, ASM is more robust
than previous methods: the use of proportional, rather than
absolute values will help to reduce the errors caused by
magnification and with a sufficiently large training set,

analysis of the modes of variation may be used to identify
and correct for rotational artefacts.

Example 2

5   A) Materials and Methods

I) Image acquisition

The same set of images was analysed as in Example 1.

II) Region Selection

10 To ensure reproducibility, the location of five regions of
interest (ROIs) was determined in relation to the centre and
angle of the narrowest part of the femoral neck and the
centre and diameter of the femoral head, as shown in Figure
3. The femoral head was described by a best-fit circle,
15 calculated from a series of manually marked points around the
outline of the femoral head. Between 15 and 20 evenly spaced
points were used to describe the outline, depending on the
size of the head. The diameter and centre (marked as F in
Figure 3) of the femoral head were then taken from this
20 circle.

The narrowest part of the neck (neck-width) was determined
using two automatic edge traces, marking the upper and lower
outlines of the femoral neck. The first point and the
25 direction for each trace were marked manually; the edge of
the neck could then be identified automatically. The neck
width (A - E) was calculated by finding the smallest
Euclidean distance between the traces. The centre of the neck
was located at the mid-point of this line (point C) and the
30 axis of the femoral neck was taken to be a line
perpendicular to this through the centre of the neck (dashed
line).

Each ROI was 256 x 256 pixels and was selected from either the upper region of the head (UH), the central region of the head (CH), the upper region of the neck (UN), the Ward's triangle (WA) or the lower region of the neck (LN). The
5 points and regions were identified using a macro written for Image Pro Plus software (version 4.1.0.0, Media Cybernetics, Silver Spring, Maryland). The top right corner of the WA region was located at the midpoint of the neck width (point C). Points B and D were placed 25% and 75% of the way along
10 the neck width and used as the midpoints of the UN and LN regions respectively. Point F, the centre of the femoral head marked the centre of the CH region and point G, the centre of the base of the UH region. Point G was placed one half of the femoral head diameter above point F, at a 45-degree
15 angle to the neck width (A-E).

III) Region Analysis

Analysis was performed using Matlab software (version 6.1.0, MathWorks Inc, Natick, Massachusetts). A fast Fourier
20 transform was generated for each ROI and three profiles were generated using data from the power spectrum. Firstly a global or circular profile (CircP) was generated, composed of the magnitude at each frequency averaged across all angles.
25
The angle of preferred orientation was calculated by finding the angle of the maximum in the power spectrum for the first 25 frequencies. The median of the values plus 90° was taken as the angle of preferred orientation for each image. As the
30 Fourier power spectrum is symmetrical, angles were calculated between 0° and 180°. Two more profiles were then generated, parallel with (ParP) and perpendicular to (PerP) the angle of preferred orientation. In this case the average value was

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calculated at each frequency from all points lying within ±5°
of the desired angle.

IV) Principal Component Analysis

5 Principal Component Analysis was used to model statistically
the shape of each set of profiles (parallel, perpendicular
and circular). After performing each PCA, a scree plot was
generated by plotting the eigenvalues (representing the
proportion of variance described by each component) against
10 the component number. The eigenvalues are associated with the
components in decreasing order, with the largest eigenvalue
associated with the first component and the smallest with the
last. In each case, the first N principal components were
selected for analysis using the scree test to find an
15 'elbow' in the slope of the plot. This is used as a
threshold between the components that contain useful
information and those that can be attributed to noise. These
components were then used as input variables for further
analysis.
20

V) Fractal Analysis

Fractal analysis was performed on each profile using a method
similar to the Fourier transform technique described by
Majumdar et al (Medical Physics 1999; 26(7); 1330-1340). The
25 average power spectrum of the circular profile was plotted
on a log-log scale, three approximately linear regions were
defined and the gradient (slope) of a straight line fitted
to each region was found; slope A, a 'coarse' slope, where
the log of the frequency is less than or equal to 1.0; slope
30 B, a 'medium' slope, where the log of the frequency lies
between 1.0 and 1.75; and slope C, a 'fine' slope, where the
log of the frequency is above 1.75. The fractal dimension
was calculated using the formula suggested by Majumdar et al:

$D_{FFT} = (7-slope)/2$.

VI) Statistical Analysis

Stepwise discriminant analysis was used to select principal
5 components that could be combined to build a linear
classifier. If the stepwise procedure failed to select any
components, the most accurate of the individual components
was chosen. The same procedure was used to discriminate
between the groups using the fractal dimension. Measurement
10 of the area under the ROC curve was used to compare the
classifiers built using the discriminant analysis.

A three way ANOVA was applied in order to determine whether
there were significant differences between the performance
15 of classifiers depending on the type of analysis, the profile
used or the region analysed. Pearson product moment
correlation was applied to examine the relationship with age,
BMI and Neck BMD for the strongest classifiers. T-tests,
correlation and ANOVA were performed using SigmaStat (version
20 2.03, SPSS Science, Chicago). Principal Component Analysis,
discriminant analysis, and measurement of the area under the
ROC curve were calculated using SPSS (version 10 SPSS
Science, Chicago).

25 B) Results

There were no significant differences between the age,
height, weight or BMI of the fracture and control groups .

Table 5 shows the area under the ROC curve (Az) for PCA
30 analysis by region of the femoral neck for the circular,
perpendicular and parallel profiles respectively.

Region	Circular (95% CI)	Parallel (95% CI)	Perpendicular (95% CI)
Upper head	0.76 (0.63-0.89)	0.57 (0.41-0.73)	0.84 (0.73-0.95)
Central head	0.59 (0.43-0.75)	0.56 (0.40-0.73)	0.84 (0.72-0.95)
Upper neck	0.72 (0.58-0.86)	0.72 (0.57-0.86)	0.67 (0.52-0.82)
Ward's triangle	0.74 (0.61-0.88)	0.61 (0.45-0.76)	0.71 (0.56-0.86)
Lower neck	0.71 (0.56-0.85)	0.55 (0.39-0.71)	0.93 (0.87-1.00)

Table 5

An overall mean value of 0.70 was observed (standard deviation 0.11), with the best results coming from the circular and perpendicular profiles. The 5 largest areas under the ROC curve were obtained by PCA of the perpendicular profile of the lower neck, upper and central head regions (see Table 6 below) (Az = 0.93, 0.84 and 0.84 respectively), followed by PCA analysis of the circular profile in the upper head region (Az = 0.76) and, finally, fractal analysis of the parallel profile in the upper neck region (Az = 0.75).

A three-way analysis of variance was used to examine differences in performance due to the region, profile or type of analysis used. It showed that overall PCA analysis performed significantly better than fractal analysis (P < 0.05) and that analysis of both the perpendicular and circular profiles performed significantly better than the parallel profile (P < 0.05). No significant differences were

found between the different regions of the femoral neck ($P = 0.241$).

Table 6						
Analysis	Profile	ROI	Az (95% CI)	R_{BMD}(p)	R_{age}(p)	R_{BMI}(p)
PCA	PerP	LN	0.93 (0.87-1.00)	0.09 (0.55)	0.14 (0.34)	-0.08 (0.58)
PCA	PerP	UH	0.84 (0.73-0.95)	0.09 (0.52)	-0.17 (0.24)	-0.03 (0.86)
PCA	PerP	CH	0.84 (0.72-0.95)	0.06 (0.70)	0.27 (0.055)	-0.11 (0.46)
PCA	CircP	UH	0.76 (0.63-0.89)	-0.16 (0.28)	-0.15 (0.29)	0.07 (0.62)
Fractal	ParP	UN	0.75 (0.61-0.89)	-0.30 (0.034)	0.25 (0.081)	-0.04 (0.78)

Table 6 shows the area under the ROC curve (Az) for each of the best 5 classifiers, and the correlation with age R_{age}, femoral neck BMD (R_{BMD}) and body mass index (R_{BMI}), and associated significance values (P).

Thus, texture analysis of standard radiographs using a fast Fourier transform can yield variables that are significantly associated with fracture after adjustment for age, body mass index and Neck-BMD. Both PCA and fractal analysis, both derived from the FFT data, could be used to discriminate successfully between the groups, PCA being stronger than fractal dimension. The best results from this study were uncorrelated with Neck-BMD, age or BMI.

PCA considerably reduces the number of variables required to characterise an image via its power spectrum. For example, in Example 2, a 256x256 pixel ROI (65,536 pixels) is

selected, the Fourier transform is generated, and a profile
of 128 spatial frequency values is generated. PCA is then
performed, and in each case was able to describe over 70 %
of the variance present in the data using only 5 components
5 or fewer. Overall, the performance of principal components
analysis was significantly stronger than that of fractal
analysis ($P < 0.01$). An advantage of PCA is the ability to
summarise the information present in the dataset with a small
number of components via an economical mapping of the
10 variance present in the data. In addition, the property of
orthogonality between these components ensures that the
variables generated are linearly independent. Benefits can
also be found by the use of a model built on the
mathematical distributions present in the data, rather than
15 expecting the data to meet a given mathematical property,
such as fitting a fractal or normal distribution.

Example 3
A) Materials and Methods
20 Data from the radiographic study of trabecular structure
described in Example 2 was reanalysed using the first 14
Fourier components, in order to simulate the lower resolution
of a DXA scan. The method employed in Example 2 was used.

25 B) Results
74% of subjects were correctly identified from the lower
resolution images (Az=0.71, 95% CI = 0.56-0.86). This is a
similar degree of accuracy as the BMD value (74% accuracy,
Az=0.79, 95% CI 0.66-0.91), and the ASM analysis (74%
30 accuracy, Az=0.81, 95% CI = 0.69-0.93).

When the low resolution result was combined with ASM and BMD
data, even more accurate results were obtained, resulting in

the ability to discriminate between fracture and control
groups with 84% accuracy (Az=0.913, 95% CI = 0.837 - 0.990).
The low resolution Fourier Transform was not significantly
correlated to either the shape, measured by the ASM
5 classifier (r=-0.716, P=0.220) or BMD (r=0.159, P=0.269).

These results thus show that measurements obtained from the
shape and trabecular structure of the femur can be applied
to DXA images, thus making it possible for these results to
10 be combined with BMD data to improve fracture risk
prediction.